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92. (New) A method according to claim 82, wherein the loci are selected on the basis of their ability to discriminate among subjects.

93. (New) A method, according to claim 77, wherein the step A' of reacting the material involves using a different reaction from that of step A and the second allele is different from the given allele.

94. (New) A method according to claim 75, wherein step (A) includes the step of assaying for the given allele using genetic bit analysis, allele-specific amplification, polymerase chain reaction, or a ligase chain reaction.

95. (New) A method according to claim 82, wherein the loci are proximal to one another, so that the set of genotypes so produced may indicate a sequence of nucleotides associated with the genetic material. - -

REMARKS

A. Summary of the Invention

Broadly, the subject invention concerns a method for determining the genotype at a genetic locus for a sample of genetic material obtained from a biological sample. The method includes a step of reacting the material at the locus to produce a first reaction value indicative of the presence of a given allele at the locus. A data set is formed which includes at least the first reaction value. The method of the invention also includes a step of establishing a distribution set

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of probability distributions associating hypothetical reaction values with corresponding probabilities for each genotype of interest at the locus. The method of the invention further includes a step of applying the first reaction value to each pertinent probability distribution to determine a measure of a conditional probability of each genotype of interest at the locus. Finally, the method of the invention includes a step of determining the genotype based on data from the step of applying the first reaction value to each pertinent probability distribution to determine a measure of the conditional probability of each genotype of interest at the locus.

B. Summary of the Outstanding Office Action

Withdrawal of prior rejections under 35 USC §112, first and second paragraphs in the Office Action of 18 January 2002 is noted.

In various art rejections set out in the Office Action of 18 January 2002, claim 50 was included among the rejected claims. However, claim 50 was cancelled without prejudice in the prior reply to an Office Action of 13 December 2001 and was no longer pending in the application at the time of the Office Action of 18 January 2002.

In the Office Action of 18 January 2002, claims 50 [*sic*] through 54 inclusive and 69 through 74 inclusive were finally rejected under 35 USC § 102(a) as unpatentable over a publication by Kimpton *et al.* in *PCR Methods and Applications*, volume 3, pages 13 through 22 (August 1993) ("the Kimpton *et al.* publication"). It was asserted that the Kimpton *et al.* publication disclosed at page 14 a method of determining the genotype at a locus within genetic material obtained by polymerase chain reaction ("PCR") amplification. With citations to pages 14 through 16 and Figures 1 and 2 of the Kimpton *et al.* publication, it was asserted that the method of the publication included (a) assembling reaction value data points for samples where each reaction value data point corresponded to a respective one of the samples and included at

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least one reaction value. It was asserted that the datapoints were represented by each of the separate peaks shown in Figure 1 of the publication and represented a different sample and that the datapoints were assembled as shown in Figure 2. It was asserted further that the method of the Kimpton *et al.* publication included a step (b) of determining an initial conditional probability for each reaction value data point for each genotype. It was asserted that the data was initially analyzed by analyzing bands to establish a conditional probability for reaction value, with a citation to page 15 and Figure 1. It was asserted further in the outstanding Office Action that the method of the Kimpton *et al.* publication included a step (c) of computing a conditional probability of each genotype for each reaction value data point. It was asserted that a calculation of band sizing determined the allele to which the sample belonged, assertedly thereby determining a genotype since assertedly a genotype was composed of particular allele at particular positions. Page 16, columns 2 and 3 and page 17, Table 2 were cited in connection with this assertion. It was asserted further that the method of the Kimpton *et al.* publication included a step (d) of determining the genotype and confidence score for each reaction valued data point, assertedly thereby determining the genotype and confidence score at the genetic locus for each sample. Table 2 on page 17 was asserted to provide for each reaction point the genotype and a standard deviation based on the data obtained from step (d).

It was asserted further in the Office Action of 18 January 2002 that the Kimpton *et al.* publication disclosed reacting material at multiple loci and disclosed multiple alleles in probability distributions. Figure 2 on page 16 was cited in connection with an assertion that the Kimpton *et al.* publication disclosed the use of multiple data points derived from multiple runs of an automated apparatus, assertedly including multiple data sets in the method and apparatus of the publication. It was asserted that the Kimpton *et al.* publication disclosed that the locus may be dinucleotide or tetranucleotide repeats and that the publication selected the loci for their discrimination ability and disclosed that several different loci may be analyzed.

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In the outstanding Office Action, claims 50 [*sic*] through 54 inclusive and 60 through 74 inclusive were finally rejected under 35 USC § 103(a) as unpatentable over the Kimpton *et al.* publication in view of a publication by Clark in *Mol. Biol. Evol.*, volume 7, pages 111 through 122 (March 1990) ("The Clark publication"). It was admitted in the outstanding Office Action that the Kimpton *et al.* publication did not disclose modification of data to iteratively improve an assay. It was asserted that the Clark publication disclosed a method of resolving ambiguities by performing an iterative cascade of improvements on data points. It was asserted that the method of the Clark *et al.* publication was applied to restriction site polymorphisms. With a reference to a passage in the abstract of the Clark publication which asserted that the algorithm of the publication applied to the problem of inferring haplotype frequencies of closely linked restriction site polymorphisms, it was asserted that an ordinary practitioner would have been motivated to apply the conceptual idea of iterative data processing of the Clark publication in the genotyping method of the Kimpton *et al.* publication in order to extract as close to the entirety of the allelic sequences as possible. It was asserted further that an ordinary practitioner would have recognized that the method could be performed using any link marker, including single nucleotide polymorphisms such as the restriction site polymorphisms assertedly disclosed in the Clark publication.

Claims 50 [*sic*] through 54 inclusive and 56 through 74 inclusive were finally rejected under 35 USC § 103(a) in the Office Action of 18 January 2002 as unpatentable over the Kimpton *et al.* publication in view of Clark publication and further in view of published International Patent Application WO 92/15712 to Goelet *et al.* ("the Goelet *et al.* '712 published international application"). It was admitted in the outstanding Office Action that the Kimpton *et al.* publication even in view of the Clark publication did not teach genetic bit analysis, which was asserted to include allele specific amplification. It was asserted that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the method of the hypothetical combination of the Kimpton *et al.* publication in view of the Clark publication with the use of genetic bit analysis or allele specific amplification to develop the data 29302.1

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in view of the Goelet *et al.* '712 international published application. It was asserted that an ordinary practitioner would have been motivated to substitute an assertedly equivalent genetic bit analysis method for PCR assertedly in order to minimize the need for gel electrophoresis and enhance the automatability of the process as assertedly motivated by the Goelet *et al.* international published application assertedly in order to speed analysis and minimize cost.

Claims 50 [*sic*] through 54 inclusive, 56, 58, and 60 through 74 inclusive were rejected in the outstanding Office Action under 35 USC § 103(a) as unpatentable under the Kimpton *et al.* publication in view of the Clark publication and further in view of United States patent No. 5,516,663 to Backman *et al.* ("the Backman *et al.* '663 patent"). It was admitted in the Office Action that the Kimpton *et al.* publication even in view of the Clark *et al.* publication did not disclose the use of a ligation chain reaction. It was asserted that the Backman *et al.* '663 patent disclosed a method of ligation chain reaction. It was asserted that it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the method of the hypothetical combination of the Kimpton *et al.* publication in view of the Clark publication with the use of a ligation chain reaction as assertedly disclosed in the Backman *et al.* '663 patent. A passage at column 2, lines 8 through 10 of the Backman *et al.* '663 patent was cited in this connection. It was asserted that an ordinary practitioner would have been motivated to substitute the ligation chain reaction for an assertedly equivalent amplification method of polymerase chain reaction with the asserted motivation that the ligation chain reaction assertedly could detect small numbers of target molecules and assertedly because ligation chain reaction was a known equivalent amplification assay to the polymerase chain reaction disclosed in the Kimpton *et al.* publication.

C. Summary of the Present Amendments
And Request for Reconsideration

New claims 75 through 95 inclusive have been added to the present response. The new claims find support in the application as originally filed, for example, at page 2, line 11 through 29302.1

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page 3, line 20 and page 12, line 5 through page 16, line 12. It is submitted that new claims 75 through 95 inclusive do not constitute new matter.

In a prior reply to an Office Action dated 13 December 2001, dependent claims 51, 52, 56, 58, 60, and 62 through 68 inclusive were amended to change the respective dependencies of the claims to reflect the cancellation without prejudice of claims upon which the dependent claims depended and the substitution of new claims for the cancelled claims. Entry of the amendments to the dependent claims was denied in the Office Action of 18 January 2002, with the comment that neither a clean copy of the amended claims nor a marked up copy of the claims showing the amendments had been provided in the reply to the Office Action. The amendments to claims 51, 52, 56, 58 60, and 62 through 68 inclusive set forth in the reply of 13 December 2001 are repeated below. A clean copy of the amended claims is attached as Appendix A and marked up copy showing the amendments is attached as Appendix B. Entry of the amendments is respectfully requested.

The subject application includes a single multiply-dependent claim, claim 71, which was presented by preliminary amendment on 15 March 2001. From the files of the attorneys for the applicants, it appears that the multiple-dependency claim fee was not paid for claim 71, although authorization to charge any necessary fees to the attorneys' deposit account was given in the preliminary amendment of 15 March 2001. A multiple-dependency claim fee is paid for the subject application with present reply.

Reconsideration of the subject application as amended above in light of the comments below is respectfully requested.

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D. The Rejection Under 35 U.S.C. § 102(a)

The Kimpton *et al.* publication disclosed automated DNA profiling, based on detection of amplified tri-, tetra-, and pentanucleotide short-tandem-repeat ("STR") loci by electrophoresis on denaturing polyacrylamide sequencing gels using automated fluorescence-based technology. According to the abstract of the Kimpton *et al.* publication, the system of the publication used an internal size standard in each sample to permit the short tandem repeat products amplified by PCR to be sized automatically. Three multiplex short-tandem-repeat systems containing a total of fourteen different loci were used, with different fluorescent markers used for loci which had overlapping allele size ranges.

According to column 3, lines 20 through 29 of page 13 of the Kimpton *et al.* publication, dinucleotide short-tandem repeats exhibited "slippage" during amplification which resulted in artifactual "stutter bands." The publication disclosed that such stutter bands made unambiguous allele designation difficult. It was stated that tri- and tetrameric repeats had a wider allele spacing and appeared to be significantly less prone to slippage, and therefore more suitable for the technique of the publication. According to column 1, lines 4 through 8 of page 16 of the Kimpton *et al.* publication, 14 three to five-base-pair short-tandem-repeat loci were selected for evaluation based on their predicted discrimination power. Upon evaluation, two of the short-tandem repeat loci selected displayed a number of allele bands which differed by one base pair and two base pairs, according to page 16, column 2, line 16 through column 3, line 14 of the publication. It was noted that although such differences could be resolved on the polyacrylamide gels, the consistency of automatic sizing between gels was not sufficient to allow precise allele designation using those loci. A direct comparison of computer generated band sizes to those of an allelic ladder control run on the same gel was required in order to assign the two loci in question.

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Concerning the technique for automatically sizing the short tandem repeat products in the procedure of the Kimpton *et al.* publication, the publication disclosed at page 16, column 1, lines 9 through 18 that amplification products of the short-tandem-repeat loci were tagged by the attachment of a fluorescent dye molecule to one of each pair of the loci-specific amplification primers. Amplification products from each of the three multiplex amplification-reaction systems were respectively electrophoresed for eight hours on a polyacrylamide denaturing sequencing gel in an automated DNA sequencer. During electrophoresis on the denaturing polyacrylamide gels, amplified products were detected by laser scanning. According to column 1, lines 17 through 34 of page 15 of the publication, fragment sizes after eight hours of electrophoresis on the automated DNA sequencer were determined using software employing a method of second order regression to establish a curve of best fit for the internal standard in each lane. Other than the reference to second order regression, internal operation of the software for determining fragment sizes does not appear to be described in the Kimpton *et al.* publication.

In contrast, new claim 75 of the subject application as amended is directed to a method for determining the genotype at a genetic locus for a sample of genetic material obtained from a biological sample which includes a step, among others, of establishing a distribution set of probability distributions associating hypothetical reaction values with corresponding probabilities for each genotype of interest at the locus. The method of the new claim 75 further includes a step of applying a first reaction value indicative of the presence of a given allele at the locus to each pertinent probability distribution to determine a measure of a conditional probability of each genotype of interest at the locus. The method of new claim 75 also includes a step of determining the genotype based on data from the step of applying the first reaction value to each pertinent probability distribution.

For the reasons set forth above, it is submitted that the automated DNA profiling method of the Kimpton *et al.* publication would have neither disclosed nor in any way suggested the method of determining the genotype and confidence scores at a genetic locus of new claim 75 of 29302.1

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the subject application. It is submitted therefore that new claim 75 is patentable over the Kimpton *et al.* publication.

New claims 76 through 95 inclusive are dependent claims which depend upon new claim 75 directly or indirectly, and consequently incorporate the limitations of new claim 75 by reference. For the reasons discussed above in connection with new claim 75, it is submitted that the Kimpton *et al.* publication would have neither disclosed nor in any way suggested the subject matter of new claims 76 through 95 inclusive. It is submitted therefore that each of new claims 76 through 95 inclusive is patentable over the Kimpton *et al.* publication and that the rejection of any of new claims 76 through 95 inclusive under 35 U.S.C. § 102(a) as unpatentable over the Kimpton *et al.* publication would be without justification.

Claim 72 of the subject application as amended is directed to a method of determining both genotype and confidence scores at a genetic locus for a plurality of samples of genetic material, where the samples have been prepared under comparable conditions. The method includes the step of assembling reaction-value data points for the samples. Each reaction-value data point is specified to correspond to a respective one of the samples and to include at least one reaction value. The method of claim 72 further includes the step of determining an initial conditional probability for each reaction-value data point for each genotype and computing a conditional probability of each genotype for each reaction-value data point. The method of claim 72 finally includes the step of determining the genotype and confidence score for each reaction-value data point, thus determining the genotype and confidence score at the genetic locus for each sample.

For the reasons set forth above, it is submitted that the automated DNA profiling method of the Kimpton *et al.* publication would have neither disclosed nor in any way suggested the method of determining the genotype and confidence scores at a genetic locus of claim 72 of the

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subject application. It is submitted therefore that claim 72 is patentable over the Kimpton *et al.* publication.

Claims 51 through 54 inclusive, as amended, 73, and 74 are dependent claims which depend upon claim 72 directly or indirectly, and consequently incorporate the limitations of claim 72 by reference. For the reasons discussed above in connection with claim 72, it is submitted that the Kimpton *et al.* publication would have neither disclosed nor in any way suggested the subject matter of claims 51 through 54 inclusive, as amended, 73, and 74. It is submitted therefore that each of claims 51 through 54 inclusive, as amended, 73, and 74 is patentable over the Kimpton *et al.* publication and that the rejection of claims 51 through 54 inclusive, as amended, 73, and 74 under 35 U.S.C. § 102(a) as unpatentable over the Kimpton *et al.* publication is without justification and should be withdrawn.

Claim 69 of the subject application is an independent claim directed to a method of determining for a plurality of samples analyzed with comparable biochemistry, a genotype and a confidence score for the genotype at a locus within genetic material. The method of claim 69 includes the step of measuring, under comparable conditions, a first reaction value for each sample which is indicative of the presence of a given allele at the locus. The method of claim 69 further includes the step of forming a data set from the reaction values and establishing initial probability distributions for the genotype of interest at the locus. The method of claim 69 further includes the step of calculating the conditional probability of each genotype of interest at the locus, by applying the first reaction value to each probability distribution in the set of probability distributions that corresponds to the first reaction value. Finally, claim 69 includes the step of determining the genotype and confidence score.

It is submitted that the method for automated DNA profiling employing multiplex amplification of short-tandem-repeat loci coupled with direct detection of amplified products on polyacronamid gels of the Kimpton *et al.* publication would have neither anticipated nor in any

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way rendered obvious the subject matter of claim 69 of the subject application. It is submitted that the rejection of claim 69 under U.S.C. § 102(a) as unpatentable over the Kimpton *et al.* publication was unwarranted and should be withdrawn.

Claims 70 and 71 are dependent claims which depend upon claim 69 directly or indirectly, and consequently incorporate the limitations of claim 69 by reference. For the reasons noted above, it is submitted that the method of the Kimpton *et al.* publication neither anticipates nor in any way renders obvious the methods of dependent claims 70 and 71 of the subject application. It is submitted that the methods of claims 70 and 71 of the subject application are patentable over the Kimpton *et al.* publication, and that the rejection of claims 70 and 71 under 35 U.S.C. § 102(a) was without justification and should be withdrawn.

E. The Rejections Under 35 U.S.C. § 103

E.1 The Kimpton *et al.* Publication in View of the Clark Publication

The Clark publication disclosed a method for resolving ambiguities in sequencing on sequencing gels alleles from PCR-amplified DNA samples from diploid individuals. The method of the Clark publication involved obtaining DNA samples from a population of diploid individuals and identifying a homozygote or a single heterozygous site on the sequencing gel. According to lines 2 through 6 on page 112 of the Clark publication, a homozygote could be recognized on the sequencing gel by a lack of ambiguous sites. Once a homozygote was found, a haplotype had been identified. Two haplotypes were identified if the individual had a single heterozygous site. The method of the Clark publication involved tallying the haplotypes identified by finding homozygotes and single heterozygous sites. As disclosed at line 7 through 12 on page 112 of the Clark publication, the method of resolving ambiguous sequences entailed determining, for each known haplotype, whether the haplotype could be made from some

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combination of the ambiguous sites. For each such haplotype, the complement of the haplotype was recovered as another potential haplotype. The process was continued until all haplotypes have been recovered or no new haplotype can be found.

It is submitted that the Clark publication in no way cures the infirmities of the Kimpton *et al.* publication as a reference against claims 51 through 54 inclusive and 69 through 74 inclusive of the subject application as amended. It is submitted therefore that the Kimpton *et al.* publication considered alone or in combination with the Clark publication would have neither disclosed nor suggested the method of claims 51 through 54 inclusive and 60 through 74 inclusive of the subject application as amended. Consequently, it is submitted that the rejection of claims 51 through 54 inclusive and 60 through 74 inclusive of the subject application under 35 U.S.C. § 103(a) as unpatentable over the Kimpton *et al.* publication in view of the Clark publication was without justification and should be withdrawn.

**E.2 The Kimpton *et al.* Publication in View of the Clark Publication
Further in View of the Goelet *et al.* '712 Published International Application**

As disclosed in the abstract, the Goelet *et al.* '712 published international application disclosed a method for determining the identity of a nucleotide base at a specific position in a nucleic acid of interest and a method for determining the presence or absence of a particular nucleotide sequence in a sample of nucleic acids. The methods entailed contacting nucleic acid of interest with an oligonucleotide primer under hybridizing conditions and treating the resulting duplex, if any, with a terminator reagent under conditions permitting base pairing of a complementary terminator present in the reagent and the occurrence of a template-dependent, primer extension reaction so as to incorporate the terminator at the 3' end of the primer. The identity of the terminator at the 3' end of the primer determined whether the hybridization occurred and the identity of the base complementary to the terminator.

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The Kimpton *et al.* publication disclosed an automated DNA profiling method which employed three multiplex groups of particular three to five-base pair short-tandem-repeat loci which were amplified groupwise by PCR and analyzed by denaturing polyacrylamide sequencing gels.

It is submitted that a person of ordinary skill in the art as of the effective filing date of the subject application would not have attempted to combine the methods of the Kimpton *et al.* publication and the Clark publication with a method of the Goelet *et al.* '712 published international application as hypothetically proposed in the outstanding Office Action, particularly since the Kimpton *et al.* publication disclosed that the method of the publication was satisfactory for its intended purpose.

It is submitted therefore that the Kimpton *et al.* publication considered alone or in view of the Clark publication or further in view of the Goelet *et al.* '712 published international application would have neither disclosed nor suggested the method of any of claims 51 through 54 inclusive and 56 through 74 inclusive of the subject application as amended and that the rejection of such claims under 35 U.S.C. § 103(a) as unpatentable over the Kimpton *et al.* publication in view of the Clark publication and further in view of the Goelet *et al.* '712 published international application should be withdrawn.

E.3 The Kimpton *et al.* Publication in View of the Clark Publication
 Further in View of the Backman *et al.* '663 Patent

The Backman *et al.* '663 patent disclosed a ligase chain reaction with a certain endonuclease correction and contamination control. The Backman *et al.* '663 patent does not appear to cure the infirmities of the Kimpton *et al.* publication and the Clark publication -- separately or in hypothetical combination as proposed in the outstanding Office Action -- as references against claims 51 through 54 inclusive, 56, 58, and 60 through 74 inclusive of the subject application as amended. It is submitted that the Kimpton *et al.* publication, the Clark 29302.1

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publication, and the Backman *et al.* '663 patent considered alone or in any combination do not disclose or in any way suggest the method of claims 51 through 54 inclusive, 56, 58, and 60 through 74 inclusive and that the rejection of claims 51 through 54 inclusive, 56, 58, and 60 through 74 inclusive as amended under 35 U.S.C. § 103(a) as unpatentable over the Kimpton *et al.* publication in view of the Clark publication and further in view of the Backman *et al.* '663 patent was not justified and should be withdrawn.

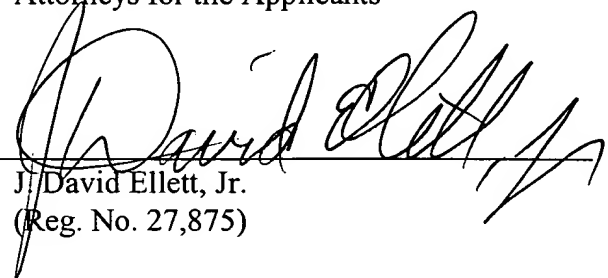
F. Conclusion

For the reasons set forth above, it is submitted that the claims of the subject application as amended meet the standards of 35 U.S.C. § 112, first and second paragraphs, and are patentable over the art of record considered alone or in any combination. Early allowance of the application is therefore earnestly solicited.

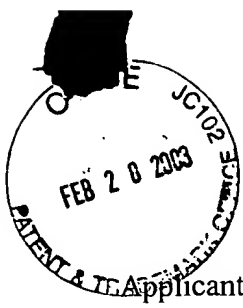
Respectfully submitted,

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**APPENDIX B**

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Marked-Up Copy of Amended Claims

51. (Amended) A method according to claim [49] 72, wherein the reaction values are measurements of an optical signal or a digital image intensity value.
52. (Amended) A method according to claim [50] 74, wherein the reaction values are measurements of an optical signal or a digital image intensity value.
56. (Amended) A method according to claim [49] 72, wherein the reaction values are obtained by assaying for alleles using a method selected from the group consisting of genetic bit analysis, hybridization, allele-specific amplification and a ligase chain reaction.
58. (Amended) A method according to claim [50] 74, wherein the reaction values are obtained by assaying for alleles using a method selected from the group consisting of genetic bit analysis, hybridization, allele-specific amplification and a ligase chain reaction.
60. (Amended) A method according to claim [48] 72, further comprising detecting the presence of a downward trend in confidence scores over time.
62. (Amended) A method according to claim [49] 72, wherein the reaction values are obtained by assaying for one or more alleles that provide information relating to a trait.
63. (Amended) A method according to claim [50] 74, wherein the reaction values are obtained by assaying for one or more alleles that provide information relating to a trait.

64. (Amended) A method according to claim [49] 72, wherein one or more of the reaction values are obtained by assaying for one or more alleles that provide information pertaining to parentage of the subject.

65. (Amended) A method according to claim [50] 74, wherein one or more of the reaction values are obtained by assaying for one or more alleles that provide information pertaining to parentage of the subject.

66. (Amended) A method according to claim [48] 72, wherein more than one genetic loci are analyzed.

67. (Amended) A method according to claim [49] 72, wherein the reaction values are obtained by assaying for one or more alleles that provide information useful for determining the identity of the subject.

68. (Amended) A method according to claim [50] 74, wherein the reaction values are obtained by assaying for one or more alleles that provide information useful for determining the identity of the subject.